REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the rejections of the claims. After entry of the amendment, claims 56, and 69-75 are pending in the application.

Applicants have cancelled claims 1-55 and 57-68 without prejudice or disclaimer. Claims 1-55 and 58-68 were withdrawn due to a restriction requirement. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications.

Claim 56 has been amended. Claims 69-76 are newly added. Support for the amended and newly added claims is found throughout the specification including page 8, line 32 to page 9, line 36; page 25, lines 10-26, page 31, lines 1-3, page 38, lines 12-18, and page 40, lines 16-21; page 38, lines 12-18; page 41, lines 28-32; page 51, lines 11-25, and pages 85-91 of the specification. Applicants submit no new matter has been introduced by the foregoing amendment.

Sequence Listing

Applicants have provided herewith a computer readable form copy of the sequence listing reflecting the disclosed amino acid sequences in Figure 32 and in the figure description on page 7 of the specification, and the amino acid sequence of PA23. A substitute paper copy of the sequence listing is also provided. In addition, Applicants have amended the specification to insert sequence identifiers.

Claim Objection

Claim 57 is objected to for alleged recitation of various therapeutic molecules drawn to non-elected inventions. To expedite prosecution of this application, Applicants canceled claim 57, thereby obviating the objection. Withdrawal of this objection is respectfully requested.

35 U.S.C. § 112, second paragraph

Claim 57 was rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner alleges the term "PA23" is vague and indefinite. Claim 57 has been

canceled. Although this rejection has not been applied to the amended and newly presented claims, it is discussed insofar as it might apply.

The Examiner required amendment of the disclosure to include the amino acid sequence of PA23 incorporated by reference and stated that amending the claims to identify the PA23 polypeptide by a sequence identifier could obviate the rejection. While Applicants do not agree with some of the statements of the Examiner concerning the sequence and accession knows. For example, Applicants note that although records in GenBank may be modified the history of the revisions of the record are available. However, in order to expedite prosecution, Applicants have amended the claims, sequence listing, and disclosure to include sequences for the nucleotide and amino acid sequence for stanniocalcin precursor(SEQ ID NO:75; SEQ ID NO:76). As required by MPEP §608.01(p), a declaration stating the amendatory material consists of the same material incorporated by reference in the referencing publication is provided herewith.

In view of the forgoing, Applicants respectfully request withdrawal of this rejection.

35 U.S.C. § 112, first paragraph

Claims 56 and 57 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. The Examiner alleges it cannot be predicted from the information in the disclosure that inhibition of the stanniocalcin glycoprotein would effectively inhibit angiogenesis and alleges use of therapeutic antibodies to treat cancer is unpredictable. Applicants have cancelled claim 57 without prejudice or disclaimer rendering the rejection of this claim moot. Applicants have amended claim 56 and respectfully traverse the rejection of claim 56.

Applicants contend that one of skill in the art reading the specification would be able to make and use the method as claimed. There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quantity of experimentation. MPEP 2164.01(a) citing *In Re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). Considerable experimentation can be required if it is routine.

Furthermore, the scope of enablement must only bear a reasonable correlation to the scope of the claims.

The Examiner alleges it cannot be predicted from the information in the disclosure that the inhibition of stanniocalcin would effectively inhibit angiogenesis. Applicants do not agree. Applicants have shown that expression of a number of different genes including the gene encoding a stanniocalcin precursor are upregulated in endothelial cells undergoing tube formation. The endothelial cell model for tube formation is an art recognized model for angiogenesis. Davis et al., Exp. Cell. Res. 224:39-51 (1996). Moreover, Applicants have provided a working example showing upregulation of stanniocalcin precursor in this art recognized model. Applicants teach that stanniocalcin precursor expression is dramatically enhanced under tube-forming conditions (*see*, Example 19, page 142 of the specification and page 25, lines 20-26 of the specification). In contrast, lower levels of stanniocalcin precursor are expressed under conditions that do not foster tube formation. Applicants contend this data demonstrates a strong correlation between expression of stanniocalcin precursor and tube-formation. Based on Applicants' findings, one skilled in the art would expect stanniocalcin precursor to play a role in angiogenesis, and that antibodies to stanniocalcin precursor would modulate angiogenesis.

The involvement of that stanniocalcin precursor in angiogenesis is confirmed by other research in the field. For example, Zlot *et al.* teach that stanniocalcin 1 modulates hepatocyte growth factor (HGF) responses, and may contribute to the maturation of newly formed blood vessels (*see*, Zlot *et al.*, 2003, *Journal of Biol. Chem.* 278(48):47654-47659, page 47658, second column, lines 40-47; copy enclosed). Zlot *et al.* teach that stanniocalcin 1 is an autocrine modulator of HGF-induced endothelial migration and morphogenesis (*see*, Zlot *et al.*, page 47658, second column, lines 11-23). Moreover, Zlot *et al.* found that in an *in vivo* model of physiological angiogenesis, the expression profile of stanniocalcin 1 mRNA resembled that of the endothelial cell marker CD31, and the peak expression of STC1 mRNA was preceded by peak expression of HGF. Wary *et al.*, found that stanniocalcin is upregulated in VEGF-activated endothelial cells (*see*, Wary *et al.*, 2003, *Molecular Cancer* 2(1):25; copy enclosed).

Consistent with the teachings of Zlot *et al.*, Filvaroff *et al.* found that stanniocalcin 1 transgenic mice had significantly higher capillary density in organs and muscles compared with age-matched wildtype littermates (*see*, Filvaroff *et al.*, 2002, *Endocrinology* 143(9):3681-3690, page 3689, first column, third paragraph; copy enclosed). Filvaroff *et al.* also found that stanniocalcin 1 transgenic mice showed a larger increase in vascularity after femoral ligation compared to wildtype littermates. Thus, overexpression of stanniocalcin 1 leads to an increase in vascularity *in vivo*. This data further supports involvement of stanniocalcin in angiogenesis.

The Examiner alleges an increase in mRNA expression does not necessarily correlate nor predict equivalent levels of polypeptide expression. Applicants do not agree. Applicants submit one skilled in the art would expect the level of mRNA expression to correlate with the level polypeptide expression. The Examiner's reference to the reference concerning the transferin receptor mRNA is not relevant to the subject matter of the present application. There is no indication in that reference that the transferin receptor has any structural or functional relationship to stanniocalcin. The general reference cited by the Examiner is also not relevant to Applicants claimed method as there also is no specific teaching concerning stanniocalcin that would raise any issue concerning the correlation of mRNA with protein expression. Moreover, Zlot *et al.* confirmed that increased mRNA levels for stanniocalcin (STC-1) in 3-D HUVECS cells was also accompanied by an increase in protein levels of STC1 in the supernatant. (See Figure 1 and p 47655, col. 2).

The Examiner alleges those of skill in the art recognize that *in vitro* assays lack correlation to *in vivo* situations. Applications request that Examiner provide evidence for this statement. Applicants remind the Examiner that only a "reasonable correlation is required" and that Examiner must give reasons for lack of correlation. Examiner has cited two general references to indicate that there may be barriers to the delivery of drugs including monoclonal antibodies into tumors. Applicants submit these general references are not relevant to Applicant's claimed invention and also are too old to properly reflect the current state of the art. One of the articles was published in 1994 and the other in 1989. Applicants submit that the art of using antibodies therapeutically has advanced significantly since that time.

The Examiner also contends that the use of therapeutic antibodies to treat cancer is unpredictable and the disclosure provides no objective evidence or working examples to establish a reasonable expectation of success in inhibiting angiogenesis *in vivo*. Applicants do not agree and submit one of skill in the art would expect that an antibody that inhibits angiogenesis *in vitro* would inhibit angiogenesis *in vivo*. Antibodies that inhibit angiogenesis *in vitro* have been shown to inhibit angiogenesis *in vivo*. For example, anti-VEGF antibodies were known to inhibit angiogenesis both *in vitro* and *in vivo* (*see*, Presta *et al.*, 1997, *Cancer Res.*, 57:4593-4599; copy enclosed). Based on Applicants' teachings and the knowledge in the art related to inhibition of angiogenesis with antibody antagonists, one skilled in the art would expect that treatment with an agent that antagonizes stanniocalcin activity would inhibit angiogenesis. Applicants teach, for example, that neutralizing antibodies to stanniocalcin are useful as therapeutic molecules because they bind to stanniocalcin and thereby remove it from the immediate cellular environment (page 25, lines 17-19). Applicants' teachings are confirmed by other research in the field. For example, Zlot *et al.* teach that stanniocalcin 1 modulates hepatocyte growth factor (HGF) responses, thereby contributing to the maturation of newly formed blood vessels (*see*, Zlot *et al.*, at page 47658, second column, lines 40-47). Therefore, one skilled in the art would have had a reasonable expectation that neutralizing or antagonizing antibodies to stanniocalcin would be useful for inhibiting tumor growth *in vivo* by preventing tumors from developing blood vessels during angiogenesis and/or vasculogenesis (page 12, lines 23-28 of the specification).

In view of the forgoing, Applicants submit the specification sufficiently teaches how to practice the claimed methods without undue experimentation. Withdrawal of the enablement rejection is respectfully requested.

35 U.S.C. § 112, first paragraph , Written Description

The Examiner rejected claim 55 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants note claim 55 has been cancelled without prejudice or disclaimer rendering the rejection of this claim moot. Withdrawal of the written description rejection is respectfully requested.

35 U.S.C. § 102(b)

The Examiner rejected claim 56 under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,733,876 ("O'Reilly *et al.*"). The Examiner alleges O'Reilly *et al.* teaches a method of inhibiting angiogenesis in a mammal comprising administering to the mammal a therapeutically effective amount of a therapeutic composition that inhibits angiogenesis. O'Reilly *et al.* does not teach each and every element of Applicants' claims. O'Reilly *et al.* does not teach inhibiting angiogenesis by administering an antibody that specifically binds a polypeptide comprising an amino acid sequence of SEQ ID NO:76 or an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:76.

In view of the forgoing, Applicants respectfully request withdrawal of the anticipation rejection.

CONCLUSION

In light of the forgoing Amendment and Remarks, Applicants assert the claims are in condition for allowance. Early notice of allowable claims is requested. The Examiner is invited to telephone the undersigned attorney for clarification of any of these Remarks or Amendments, or to otherwise speed prosecution of this case.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903

Date: September 2, 2004

Katherine M. Kowalchyk

Katherine M. Kowalchyk
Reg. No. 36,848